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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/283,431	04/01/1999	WEN-QIANG ZHOU	475.08.423	9988
7590	03/02/2005		EXAMINER	
WAYNE A KEOWN			VIVLEMORE, TRACY ANN	
HALE & DORR				
60 STATE STREET			ART UNIT	PAPER NUMBER
BOSTON, MA 02109			1635	

DATE MAILED: 03/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	ZHOU ET AL.
09/283,431	
Examiner	Art Unit
Tracy Vivlemore	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 24 November 2004.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 4-11 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 4-11 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)
2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 11/04.

4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
5) Notice of Informal Patent Application (PTO-152)
6) Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Double Patenting

Claims 4-11 are maintained as provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of copending Application No. 10/291,058. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims 4-11 are directed to oligonucleotides encompassed entirely in the claims of 10/291,058 and are directed to oligonucleotides which are disclosed in the co-pending case as the preferred embodiments of the claimed oligonucleotides.

Applicant has correctly noted that a provisional obviousness-type double patenting rejection will be withdrawn when it is the only remaining rejection. However, until this should happen it is proper that the provisional obviousness-type double patenting rejection is maintained.

Claim Rejections - 35 USC § 103

Claims 4-11 are maintained as rejected under 35 U.S.C. 103(a) as being unpatentable over Metelev et al. (US 6,143,881) in combination with Ghosh et al. (reference B1 on PTO form 1449, filed April 24, 2000).

Claims 4-6 are drawn to oligonucleotides that consist of a region of deoxyribonucleotides comprising alternating phosphodiester and phosphorothioate internucleoside linkages and one or more regions of 2'-O-substituted ribonucleotides, and further wherein the oligonucleotides comprise between 12 and 50 or 17 and 35 nucleotides. The specification discloses alternating linkages that encompass any regular or irregular pattern of phosphodiester and phosphorothioate internucleoside linkages. Claims 7-11 further limit claim 4 to oligonucleotides wherein the phosphodiester and phosphorothioate linkages are present in ratios in the range of 1:3 to 3:1 or alternate one to one, two to one, one to two, two to two or three to three and wherein the regions of 2'-O-substituted ribonucleotides are connected by phosphorothioate or phosphodiester internucleoside linkages.

Metelev et al. teach hybrid oligonucleotides that comprise a region of 2'-O-substituted ribonucleotides at the termini of a region of deoxyribonucleotides, wherein the regions of 2'-O-substituted ribonucleotides are connected by internucleotide linkages that are linked by a mixture of phosphorothioate and phosphodiester linkages. The oligonucleotides taught by Metelev et al. comprise 12-50 and 17-35 nucleotides and the phosphodiester and phosphorothioate linkages are present in ratios in the range of 1:3 to 3:1 or alternate one to one, two to one, one to two, two to two or three to three and wherein the regions of 2'-O-substituted ribonucleotides are connected by phosphorothioate or phosphodiester internucleoside linkages. Metelev et al. do not explicitly teach an embodiment wherein the mixture of phosphorothioate and

phosphodiester linkages occurs within the deoxyribonucleotide region of the oligonucleotide.

Ghosh et al. teach phosphorothioate-phosphodiester oligonucleotide co-polymers, including oligonucleotides that have alternating phosphorothioate and phosphodiester linkages with the same pattern as the preferred embodiments disclosed in the instant application and within the ratio of 1:3 to 3:1 and about 1:1. Ghosh et al. disclose embodiments wherein the POPS blocks include phosphorothioate and phosphodiester bonds alternating in the manner claimed (see for example Table 1). The oligonucleotides taught by Ghosh et al. comprise between 12-50 and 17-35 nucleotides. Ghosh et al. do not teach a region of 2'-O-substituted ribonucleotides in a phosphorothioate-phosphodiester oligonucleotide co-polymer.

It would have been obvious to one of ordinary skill in the art to make a hybrid oligonucleotide comprising a region of alternating phosphorothioate and phosphodiester linkages, as taught by Ghosh et al., with a region of 2'-O-substituted ribonucleotides, as taught by Metelev et al. Metelev et al. provide a motivation to do so, teaching that hybrid oligonucleotides comprising phosphorothioate and phosphodiester linkages and 2'-O-substituted ribonucleotides and deoxyribonucleotides regions have superior properties of duplex formation, RNase H activation and nuclease resistance when used as an antisense molecule. Ghosh et al. also provide a motivation, teaching on page 31 that "Overall, a co-polymer seems best for antisense applications with the (PS-PO) oligomer having the best combination of properties". One of skill in the art would have had a reasonable expectation of success in combining the teachings of Metelev et al.

and Ghosh et al. because the ability to synthesize oligonucleotides containing 2'-O-substituted sugars and both phosphorothioate phosphodiester linkages and in any pattern was routine in the art at the time of invention.

Therefore, the invention of claims 4-11 would have been obvious, as a whole, to one of ordinary skill in the art at the time the instant invention was made.

Response to Arguments

Applicant argues that there is no motivation to combine the references to obtain the instant invention and assert that the supposed common purpose of both Ghosh et al. and Metelev et al. is "an improved antisense molecule" and that improvements do not constitute a common purpose. Applicant further states that the Examiner relies on Metelev et al. to teach 2'-OMe modifications that have increased duplex stability while Ghosh et al. is relied upon to teach oligonucleotides having increased nuclease resistance. This is not persuasive, as Metelev et al. is not relied upon solely to teach 2'-OMe modifications, but also to teach oligonucleotides containing both phosphorothioate and phosphodiester linkages and Metelev et al. teach in their abstract that the oligonucleotides of their invention have increased nuclease resistance. Ghosh et al. is relied upon to teach that co-polymers of phosphorothioates and phosphodiesters are improved antisense molecules that have increased nuclease resistance. Since each of Metelev et al. and Ghosh et al. teach oligonucleotides having increased nuclease resistance they do share a common purpose that would make their combination to

produce new oligonucleotides also having the same property of increase nuclease resistance obvious to the person of ordinary skill in the art.

Applicant further assert as evidence of lack of motivation that the instant application shares a common inventor with the Metelev et al. reference and that this inventor's actual knowledge of the teaching of Metelev et al. did not lead to the instant application until the time of filing of the instant application. This argument is not persuasive because it is, as applicant states, circumstantial evidence and since it is not supported by a sworn affidavit by the common inventor the Examiner is unable to answer these assertions.

Applicant asserts that one of ordinary skill in the art would have no reasonable expectation of success in combining the teachings of Metelev et al. and Ghosh et al. This is not a persuasive argument as reagents for chemical synthesis of oligonucleotides containing 2'O-substituted sugars and phosphorothioate and phosphodiester linkages are commercially available and their use with automated DNA synthesizers was well-known and routine in the art at the time of invention.

Applicant has previously argued that the instant application discloses oligonucleotides made according to the instant invention which demonstrate unexpected results that rebut a finding of obviousness and have amended to the claims in an attempt to overcome the previous Examiner's statement that the evidence of unexpected results is not commensurate in scope with the claims. However, the previous Examiner stated that the applicant's argument regarding unexpected results not only was not commensurate in scope with the claims but also did not provide data to

show how the results are unexpected. The amendment does not address the lack of data. It is further noted that applicant's prior arguments regarding unexpected results do not appear in the prior art or in a sworn declaration and hence cannot be adequately answered.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Art Unit: 1635

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see <http://pair-direct.uspto.gov>.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Tracy Vivlemore
Examiner
Art Unit 1635

TV
February 28, 2005



SEAN MCGARRY
PRIMARY EXAMINER